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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,134	01/23/2002	Jean-Claude Sonntag	4-31102A	2734

1095 7590 03/11/2004

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	**PAPER NUMBER**
1615	

DATE MAILED: 03/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/048,134	SONNTAG ET AL.	
	Examiner	Art Unit	
	Gollamudi S Kishore, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed on 11-10-03 is acknowledged.

Claims included in the prosecution are 1-7.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunter (WO 98/24427 in combination with Lasic (Journal of Controlled Release, 1997) both are of record.

Hunter teaches that epothilones and Taxanes are microtubule disrupting agents and suggests the use of liposomes as carriers for these compounds (note page 8, lines 15-16), page 32, line 26 through 29). Instant invention therefore, is an obvious extension of Hunger's teachings. One of ordinary skill in the art would be motivated to use art well known liposomes as carriers for epothilones with a reasonable expectation of success.

Lasic teaches various applications of liposomes because of their advantages as carriers. According to Lasic, encapsulation of toxic drugs in liposomes greatly reduces their toxic side effects. Lasic further teaches that since conventional liposomes are

removed by reticuloendothelial system (RES), one can stabilize the liposomes using polyethylene glycol thereby increasing their blood circulation time (note the abstract, pages 204-208).

The use of liposomes as carriers for epothilones would have been obvious to one of ordinary skill in the art since such a use would reduce the toxicity of the drug as taught by Lasic. The use of PEG liposomes would have been obvious to one of ordinary skill in the art since PEG-liposomes have longer circulation time in the blood.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Hunter discloses a long list of active agents including epothilones. Applicant further argues that there are 43 examples in Hunter and neither epothilones nor liposomes are mentioned. These arguments are not found to be persuasive. Hunter's teachings concern with microtubule disrupting agents and Hunter specifically teaches epithilones and Taxanes among others as two of the microtubule disrupting agents and provides examples using paclitaxel. Page 8 referred to by the examiner teaches only a handful of anti-microtubule agents. Furthermore, the studies reported in Figure 13 H deal with Epothilone B. The examiner does not consider this as 'picking and choosing'. Although Hunter does not specifically show through examples liposomes as carriers, the reference is suggestive of the use of liposomes as carriers and the secondary reference of Lasic shows the advantages of using liposomes as carriers. On page 207 (col. 2), Lasic reports complete remission of implanted tumors in a mouse model using sterically stabilized liposomes. Therefore, it is the examiner's position that one of ordinary skill in the art would be motivated to encapsulate a

microtubule-disrupting agent such as epothilones with a reasonable expectation of success.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the suggestion to use liposomes for microtubule disrupting agents comes from the reference of Hunter itself and that of Lasic shows the art known advantages of liposomes.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

3. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hunter (WO 98/24427 of record by itself or in further combination with Lasic (Journal of Controlled Release, 1997) as set forth above, further in view of Boni (5,683,715) also of record.

The teachings of Hunter and Lasic have been discussed above. In essence, Hunter is suggestive of the use of liposomes as carriers for the microtubule disruptive agents such as Taxanes and epothilones and Lasic teaches the rationale for the use of liposomes and sterically stabilized liposomes. What is lacking in these references is the preparation of the composition in a dry form.

Boni discloses the liposomal formulations containing the microtubule disruptive agent, taxane. Boni teaches that bioactive molecules entrapped within the liposomes have enhanced therapeutic index and improved biodistribution and reduced toxicity. Boni further teaches that for storage, the liposomes can be dehydrated and reconstituted when desired (abstract, col. 5, line 26 through col. 6, line 48).

One of ordinary skill in the art would be further motivated to use liposomes as carriers for microtubule disrupting agents, epothilones, with a reasonable expectation of success, since the reference of Boni shows the effectiveness of the liposomes for the microtubule disruptive agent, taxane. The preparation of the composition in a dry state would have been obvious to one of ordinary skill in the art since in such a form it can be stored and reconstituted when desired as taught by Boni.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant's arguments with regard to Hunter and Lasic have been

discussed above. Applicant argues that Boni is directed to Taxanes and there is no suggestion or teaching of epothilones. This argument is not found to be persuasive since as pointed out above, Hunter discloses both Taxanes and epothilones as anti-microtubule agents and one of ordinary skill in the art would be motivated to use epothilone which is also an anti-microtubule agent since the reference of Boni shows the effectiveness of the liposomes as carriers for the anti-microtubule agent, taxane, with the expectation of obtaining at least similar results.

4. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1234.

GSK

Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615